This guidance was written prior to the February 27, 1997 implementation of FDA's Good Guidance Practices, GGP's. It does not create or confer rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both. This guidance will be updated in the next revision to include the standard elements of GGP's.

GUIDANCE FOR THE PREPARATION OF THE ANNUAL REPORT TO THE PMA APPROVED HEART VALVE PROSTHESES

INTRODUCTION:

Annual post-approval reports to the PMA required under 21 CFR 814.84, are necessary for the continued approval of the PMA. The data required under 814.84 include the following:

1. any changes described under 814.39 (a) and any changes required under 814.39 (b); and

2. summary information related to the clinical use of the device and/or bibliography of information not previously submitted.

Item #1 refers to such changes as labeling and manufacturing changes that may or may not also require a supplement to the PMA. Item #2 refers to all adverse information data that the sponsor has learned of, in the preceding year.

The annual report should be divided into 2 main sections as described above. Section 1 should include those changes as identified under 814.39 (a) and (b) in chronological order. Section 2 should detail the clinical reports of adverse reactions, complications, malfunctions, etc. learned in the preceding year.

Section 2 - Purpose and Essential Elements:

Purpose:

The purpose of the remaining portion of this guidance is to explain how an applicant should compile the information referred to in item #2, the adverse reaction reports section of the annual report, as it pertains to heart valve prostheses.

Essential Elements:

Clinical Data:

Although manufacturers are not required, for the purpose of the annual report, to report adverse reactions already reported to the Mandatory Device Reporting (MDR) system, they are strongly encouraged to do so. An efficient and accurate review is

otherwise not possible if the information in the annual report is incomplete.

The annual report should include those reactions which were previously defined in the PMA as well as newly recognized reactions not defined or observed in the PMA clinical data. These reactions should be those made known to the sponsor to have occurred in the preceding annual interval.

The annual report should contain all reports of adverse reactions from any source, foreign or domestic, including information derived from commercial marketing experience, postmarketing clinical surveillance and epidemiologic studies, reports in the scientific literature and unpublished scientific papers.

The essential data pertaining to the adverse reaction in question should be reasonably complete (i.e. in the case of death an autopsy or final diagnosis should be available). The criteria used to determine whether or not the reaction was valve related should be clearly stated. The criteria should be consistently applied to all adverse reactions screened by the sponsor.

Quantitative Data:

In order to effectively review and quantify the adverse reaction data in the annual report, an estimator of numerator and denomonator should be established.

Numerator:

The numerator in the report should represent the total number of reported adverse reactions that the sponsor has been made aware of during the calender year. It should include all reports in the literature as well as reports directly made to the sponsor.

Denominator:

The denominator should represent the effective number of valves at risk in a given calender year. The denominator is an estimate derived either from sales data, or implant data or both. Once established it should not vary considerably from year to year notwithstanding appropriate adjustment due to increases or decreases in production or implant rates.

Other assumptions:

It may be necessary to include in the denominator estimate other important assumptions such as operative and long term mortality and adjust the denominator accordingly.

Incidence rates:

Annual as well as cumulative (since approval) incidence rates should be reviewed and evaluated against the PMA cohort rates (assuming a representative PMA sample of patients). Annual rates should be compared to the preceding annual interval or to the PMA cohort in the case of the first annual report. Both gross counts of adverse reactions as well as specific rates should be submitted. In order to facilitate review of the report, once a reporting format has been established and accepted, each annual report should conform to the specified format thereafter.

In the event that the valve has a variety of models and or significant options (i.e. teflon vs. dacron cuffs, extended vs. standard sewing rings), the adverse reactions should be stratified by that variable that differs from the standard valve.

ADDITIONAL POST-APPROVAL STUDIES:

It may also become necessary for the sponsor to conduct a post-approval study prospectivly on a selected cohort of patients in order to address deficiencies (although this need not be the case at all times) existing in the PMA at the time of recommedation for approval. Such areas of interest might include long term questions of durability, immunogenicity, effects of anticoagulation, etc. These deficiencies may have been brought to the sponsor's attention at any time during the approval process by either the panel, FDA or both. Such studies should always include at least the following elements:

a. a set of clear and reasonable study objectives with realistic safety and efficacy endpoints, such as, lack of evidence (by cardiac catheterization or echocardiography) of regurgitation or stenosis as an efficacy endpoint and acceptable complication rates as a safety endpoint;

b. a sample size estimate with supporting rationale;

c. clear plans for study conduct, follow-up and data collection including provision for systematic clinical assessments; and

d. a plan for appropriate statistical analysis of the data.

The Division of Cardiovascular Devices (DCD) welcomes suggestions to improve the information contained in this document. Please direct inquiries to Cathleen Michaloski, BSN, MPH at (301) 427-1200.